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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,547	10/17/2001	Jim Wells	SUNESIS.002DV1	8070

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/981,547	WELLS ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58,59,61-66 and 81-96* is/are pending in the application.

4a) Of the above claim(s) *62-64,66,90-92 and 94* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58, 59, 61, 65, 81-89, 93, 95 and 96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed June 3, 2004 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 58, 59, 61-66 and 81-87 were pending. Applicants amended claims 58, 59, 61, 82, 86 and 87. In addition, Applicants added claims 88-96. Therefore, claims 58, 59, 61-66, 81-96 are currently pending.

4. Claims 62-64, 66, 90-92 and 94 are drawn to non-elected species and/or inventions and thus these claims are/remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim.

5. Therefore, claims 58, 59, 61, 65, 81-89, 93, 95 and 96 are examined on the merits in this action.

Withdrawn Objections/Rejections

6. The objection to claim 87 is withdrawn in view of Applicants arguments and/or amendments. The rejections under 35 U.S.C. 112, second paragraph are withdrawn in view of Applicants' arguments and/or amendments. All other rejections and/or objections are maintained as discussed below.

Maintained Rejections

Claim Rejections - 35 USC § 103

7. Claims 58, 59, 61, 65 and 81-89, 93, 95 and 96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (WO 98/11436) (Date of Patent is **March, 1998**) (see IDS, entry No. 9) and Siuzdak (Siuzdak, G. Mass Spectrometry for Biotechnology. New York: Academic Press. **1996**, pages 119-126).

For ***claims 58, 86-87***, Kim et al. (see entire document) disclose a method for identifying a ligand that binds to a target protein with the greatest affinity by employing a combinatorial library of non-oligomeric organic compounds using "tethering" techniques (see Kim et al., page 1, paragraph 1; see also page 2, paragraphs 1-2). For example, Kim et al. disclose **[a]** combining said target protein with a library containing at least two non-oligomeric ligand candidates wherein said ligand candidates each comprise a disulfide bond under disulfide exchange conditions, in the presence of a reducing agent (e.g., see Kim et al., see also page 11, paragraph 2, "As obtained, a target molecule might also include a binding partner (such as a sulfur moiety within a cysteine residue) which is

available or can be made available (e.g., as a free sulfhydryl group or sulfur that is available for disulfide bond formation through exchange) for binding with a reactive moiety. If such a target molecule is used, potential ligands [i.e., at least 2] can be modified to include a free sulfhydryl group or a sulfur that is available for disulfide bond formation through exchange ... Here, non-specific binding of target molecule and potential ligands occurs through formation of a disulfide bond"; see also page 17, paragraph 1 disclosing the use of reducing agents, "non-specific interaction (here, disulfide bond formation) can be varied by adjusting the concentration of external ... reducing agents ... for example ... glutathione"). Furthermore, Kim et al. disclose the formation of a target protein-ligand conjugates (e.g., see Kim et al., claims 1-2; see also page 3, paragraphs 2-3; see also page 9, line 14; see also page 14, paragraph 1; see also page 28, paragraph 1, "This experiment illustrates under conditions wherein a specific interaction between a target molecule and ligand can take place, preferential formation of disulfide-mediated ligand-target heterodimers [i.e., a target protein-ligand conjugate] can be observed"). Furthermore, Kim et al. disclose that the target-ligand conjugate can be separated from the mixture (e.g., see Kim et al., page 3, lines 24-26, "Optionally, the complex of the ligand specifically bound to the target molecule can be separated or removed from the library or collection").

In addition, Kim et al. disclose **[c-d]** the detection of the "most abundant" target protein-compound conjugates and the identification of the non-oligomeric organic compounds present in said conjugates having the "greatest relative affinity" (e.g., see Kim et al., page 17, lines 16-25, "The direct thermodynamic relationship also provides an

alternative strategy for identifying ligands from a combinatorial library; molecules that bind with ***higher affinity*** will necessarily increase the effective concentration of the other members of the binding pair to a greater extent. Thus, in this embodiment, tethered ligands that bind with higher affinity will have disulfide bonds that are ***more resistant to reduction*** by external reducing agents, such as reduced glutathione"; see also Example 1, especially page 26, last paragraph wherein Glutathione is used in different "ratios" to determine the ligand with the highest affinity, "The biotinylated SH3 domain derivatives and the corresponding synthetic linkers (SH3 : linker; 1:10) are incubated with the library of compounds, in Tris buffer (10 mM, pH 7.5), in the presence of a redox system (e.g., reduced glutathione (GSH) and oxidized glutathione (GSSG) ***at various ratios***"). In other words, only the non-oligomeric organic ligands with the "highest affinity" will remain resistant to the highest "ratios" of reduced/oxidized glutathione. Consequently, the method would also identify the most abundant target protein-compound conjugate because, at least for the highest ratios of reduced/oxidized glutathione, the conjugate formed using the "non-oligomeric organic compound having the greatest relative affinity" would be the only one that exists at the higher rations or reduced/oxidized glutathione. Finally, Kim et al. disclose "determining the identity" of the non-oligomeric ligand present in said target protein-ligand conjugate (e.g., see Kim et al., abstract, "Non-specific affinity enhancement as a method of identifying and detecting members, such as ligands ... in a collection or library of potential ligands"; see also Summary of the Invention; see also page 8, lines 18-20).

For ***claims 59, 61, 88 and 89***, Kim et al. does not explicitly state that the ligands are "less than about 2000 daltons in size" or "less than 1500 daltons " or "less than 750 daltons" (see claims 58, 59 and 61), but Kim et al. does disclose ligands selected from the group consisting of "small organic molecules, pharmaceuticals, toxins" (see Kim et al., page 21, lines 15-20; see also claim 3 further disclosing "steroids, hormones, caffeine, ATP, cyclosporin, cyclophilin"), which would encompass molecules that are less than 750 daltons in size. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claims 65 and 93***, Kim et al. does not explicitly state that the target protein is a "TNF receptor" (e.g., see claim 65), but Kim et al. does disclose ligands that are "membrane proteins", which would encompass proteins like TNF receptors because TNF receptors are "membrane proteins" (e.g., see claims 12, 43). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference.

See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claims 81, 82***, Kim et al. teach obtaining a target protein comprising a –SH group, masked –SH group, or activated –SH group (e.g., see Kim et al., claims 1-2, "target molecule, as obtained or as modified, contains one member of a binding pair ... wherein the binding partner and the reactive moiety are each a free sulfhydryl group [i.e., an –SH group] or a sulfur moiety which is available for disulfide bond formation through exchange"; see also page 3, paragraphs 2-3; see also page 11, line 11 wherein a "cysteine" residue is disclosed).

For ***claims 83-85, 95 and 96***, Kim et al. do not explicitly state that the library must comprise "at least 25 members" or "at least 100 members" (see claims 84-85), but Kim et al. do state that libraries are produced using the split and pool synthesis techniques taught by Lam (e.g., see Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J., "A new type of synthetic peptide library for identifying ligand-binding activity" Nature **1991**, 354, 6348, 82-4), which teaches the formation of libraries with greater than 100 members. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

The prior art teachings of Kim et al. differ from the claimed invention as follows:

For ***claim 58 and 86***, Kim et al. is deficient in that it does not specifically teach the use of mass spectrometry.

However, Siuzdak teaches the following limitations that are deficient in Kim et al.:

For ***claims 58 and 86***, Siuzdak (see entire document) teaches the use of electrospray mass spectrometry to study both "non-covalent" and "covalent" antibody-antigen interactions including fragmentation techniques like MS^2 and MS^3 (see pages 119-126, especially figures 6.3-6.6 and Table 6.1).

It would have been obvious to one skilled in the art at the time the invention was made to "identify" target/ligand interactions using the method steps as taught by Kim et al. in conjunction with the mass spectrometer techniques as taught by Siuzdak because Siuzdak explicitly shows that the technique can be applied to both "covalent" and "non-covalent" including antibody-antigen interactions (see Siuzdak, figures 6.3, 6.5; see especially paragraph bridging pages 125-126, "Electrospray mass spectrometry has also demonstrated its potential in the analysis of non-covalent interactions between an antibody and a hapten, and for observing covalent protein-bound intermediates in an antibody-catalyzed reaction"), which would encompass the "antibody-antigen" complexes disclosed by Kim et al. (e.g., see Kim et al., page 4, lines 7-8 disclosing antibody-antigen reactions; see also lines 18-19 disclosing both "covalent" and "non-covalent" interactions). Furthermore, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Siuzdak with the antibody-antigen

conjugates as taught by Kim et al. (or any other target-ligand interaction) because Siuzdak explicitly states that electrospray has "demonstrated its potential" for these systems (see Siuzdak, page 126, paragraph 1).

Furthermore, one of skill in the art would be especially motivated to use mass spectrometry as disclosed by Siuzdak et al. with the "antibody-antigen" complexes as described by Kim et al. because Siuzdak et al. discloses that BOTH "covalent" and "non-covalent" interactions can be measured (and distinguished) using a mass spectrometer (see Siuzdak et al., page 123, paragraph 3, "Declusterin potentials on the order of 70 V or greater usually promote the dissociation of noncovalent complexes as well as covalent fragmentation, while lower potentials (<70 V) are conducive to the observation of noncovalent complexes (protein complexes have been analyzed at declustering potentials of 40 V). In order for the method of Kim et al. to work the modified antibodies must bind "covalently" to their respective antigens (see Kim et al., figure 1 disclosing the covalent attachment of an antigen to a sulfhydryl group on the modified antibody). Therefore, any analytical technique that can confirm the "covalent" attachment of the antigen to the modified antibody is particularly useful. Consequently, a person of skill in the art would be motivated to "identify" even a "known" ligand using a mass spectrometer to determine the type of interaction (i.e., covalent v. non-covalent) to ascertain whether the modified ligand is truly able to bind to its respective target via a "covalent" bond as required by the method. Consequently, a person of skill in the art would be motivated to search for the "modified" ligands and/or targets as disclosed by Kim et al. with electrospray mass spectroscopy as disclosed by Siuzdak et al. to find

modified ligands that can "covalently" bind to the targets as opposed to any unwanted "non-covalent" interactions that might occur.

Finally, one of ordinary skill in the art would have reasonably expected to be successful because Siuzdak shows many examples of target-ligand interactions that have successfully been analyzed on a mass spectrometer including antibody-antigen (e.g., see figures 6.3 and 6.5).

Response

8. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that elements of claims 58, 86 and 87 are not taught by the cited references (e.g., see 3/11/04 Response, page 7, paragraphs 2-3 wherein the "most abundant conjugates" and "highest affinity ligand" elements are recited).

[2] Applicants argue that Siuzdak does not explicitly state that electrospray mass spectrometry has demonstrated its potential for identifying ligands present in a covalent conjugate between a target protein and a ligand of the protein (e.g., see 3/11/04 Response, page 7, second to last paragraph).

[3] Applicants argue, "Observing a chemical entity, such as a protein-bound intermediate, and determining the identity of such chemical entity are two different things" (e.g., see 3/11/04 Response, page 7, second to last paragraph).

[4] Applicants argue, "Accordingly, Siuzdak et al. does not provide the motivation relied upon by the Examiner for making the combination relied upon in the present rejection" (e.g., see 3/11/04 Response, page 7, second to last paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees. The use of reduced/oxidized glutathione at various "ratios" would identify the "non-oligomeric organic compound having the greatest relative affinity" because only this non-oligomeric organic compound would be "resistant" to the highest ratios of reduced/oxidized glutathione. Consequently, the method would also identify the "most abundant" target protein-compound conjugate because, at least for the highest ratios of reduced/oxidized glutathione, the conjugate formed using the "non-oligomeric organic compound having the greatest relative affinity" would be the only one that exists at these higher rations of reduced/oxidized glutathione.

[2] The Examiner respectfully disagrees. Siuzdak does explicitly state that electrospray mass spectrometry can be applied for the identification of ligands present in a covalent conjugate between a target protein and a ligand of the protein (e.g., see figure 6.5, wherein single chain antibody is shown to be covalently bound to the antibody and said "conjugate" is identified in the figure i.e., the MW at 26,666 Da).

[3] Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Here, Applicants have not set forth why "observing" and "determining the identity" are two different things with respect to the Siuzdak reference? In addition, the Examiner argues that Siuzdak

teaches both (e.g., see figure 6.5 wherein the "observed" peak at 26,666 Da was used to "determine the identity" of the bound substrate as shown in the figure i.e., its "identity" is shown in the figure expressed using a chemical formula). In addition, Siuzdak also teach the use of MS^2 and MS^3 that could also be used to "determine the identity" of a bound substrate/ligand.

[4] Applicants' arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Here, Applicants never state why Siuzdak does not provide adequate motivation to combine the references. In fact, Applicants never addressed the issue of "motivation" at all.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
September 6, 2004

BEN[illegible]
PRIMARY EXAMINER